Editorials

Genetic Heterogeneity and Clinical Disease

THE CORRECT CLASSIFICATION of a hereditary disease is critical for the study of its pathogenesis. It is particularly important to evaluate genetic diseases clinically because each distinct clinical subtype may correspond to a particular mutation or limited set of mutations in the human genome. If a simple relationship can be shown between a mutation (the genotype) and the resulting clinical pattern of disease (the phenotype), early prediction of prognosis becomes possible based on analysis of deoxyribonucleic acid (DNA) alone. Moreover, different mutations may suggest different mechanisms of disease pathogenesis, which in turn may allow therapies tailored to each disease subtype.

Different mutations may be associated with a phenotype that, at first glance, is uniform (genetic heterogeneity). The mutations may be clustered at a single genetic locus or may even affect different genes. Some diseases are essentially homogeneous: sickle-cell disease in Africa is caused by a single mutation. Other disorders are remarkably heterogeneous—more than 40 mutations have been detected in the *CFTR* gene to produce cystic fibrosis. Although some of these mutations are more commonly associated with the development of pancreatic insufficiency, many *CFTR* mutations produce indistinguishable phenotypes.

In this issue Gardner reviews the evidence for genetic heterogeneity in autosomal dominant polycystic kidney disease, Alport's syndrome, and medullary cystic kidney disease, three common hereditary renal disorders.[1] Careful evaluation of the clinical patterns of these disorders shows that none of them are homogeneous. Evaluation of the pattern of inheritance of the three disorders indicates that they are also genetically inhomogeneous. In the case of autosomal dominant polycystic kidney disease, the mutations in the genes of some families are clearly linked to genetic markers on the short arm of chromosome 16,[2] although the mutated gene has not been cloned. In a minority of families, perhaps 5%, the mutation is not found on chromosome 16.[3] Initial evaluation suggested that the pattern of disease is the same whether the mutation resides on chromosome 16 or elsewhere. More detailed characterization, however, reveals a striking difference in the age of onset of end-stage renal failure in the two groups.[4] The chromosome 16-linked mutations seem to produce a much more severe form of the disease with earlier onset and a higher incidence of hypertension than the non-linked form. Although the overlap in age of onset between the two groups is such that the site of the mutation cannot be used to provide an accurate prediction of the age at which renal replacement therapy will be required, a cautious optimism is warranted in persons who have the nonchromosome 16 form, many of whom will live a normal life span without therapy.

Of the inherited renal diseases, Alport's syndrome is the only one for which a molecular basis has been found.[5,6] In three kindreds from Utah, Barker and co-workers[6] found mutations in the α5(IV) isoform of basement membrane collagen. The gene that encodes this collagen, designated *COL4A5*, is found on the X chromosome, explaining the sex-linked pattern of inheritance frequently observed in Alport's syndrome pedigrees. The availability of a genetic marker for the *COL4A5* gene enables analysis of the correlation between the genotype and phenotype in this clinically heterogeneous disease. Sensorineural deafness, lenticonus, and platelet abnormalities, all of which accompany nephropathy in a subset of patients, are prime areas for study. Certain correlations between the clinical pattern of Alport's syndrome and the associated mutation are already becoming apparent. Antignac recently showed that the presence of esophageal leiomyomas in Alport's syndrome correlates with deletions of *COL4A5* that extend upstream of the gene (C. Antignac, MD, INSERM, Paris, oral communication, August 1991). She postulates that these deletions disrupt a second gene or genes upstream of *COL4A5* to produce susceptibility to leiomyomatosis. A small fraction of patients with Alport's syndrome develop antiglomerular basement membrane antibodies after heterologous renal transplantation. Kashtan has evidence that a high proportion of such patients have extensive deletions of the *COL4A5* gene (C. E. Kashtan, MD, University of Minnesota, oral communication, August 1991). Presumably absence of the α5(IV) collagen isoform in the recipient of the graft accounts for the failure to develop immunologic tolerance to this molecule.

In his review Gardner points out that the advent of molecular analysis of genetic disease and the predictive testing that it makes possible have far-reaching ethical implications. The ethical issues in genetic testing are particularly complex for several reasons, but perhaps the most important of these is that the ramifications of a genetic diagnosis go beyond the individual member to the extended family: the diagnosis of polycystic kidney disease in a single at-risk individual often affects dozens of family members, including some who have no close links with the proband. Frequently, even close family members have no idea that they are at risk. The duty of the physician in these instances has not been resolved adequately.[2] Much depends on the nature of the particular disease in question and the benefits (and disadvantages) of diagnosis. The need for research into the use and ethical implications of testing is apparent. The problem is not, however, simply a result of the advent of molecular analysis. After all, in the case of autosomal dominant polycystic kidney disease, for example, presymptomatic diagnosis by excretory urography has been available for decades. Nevertheless, the problem has been brought into focus by the development of tests based on DNA, which are easily performed and, because of their novelty and apparent power, are appealing to patients and their physicians. It is inevitable that their use will grow rapidly. A systematic evaluation of the effects of these tests on individuals and on society as a whole is timely.

Genetic heterogeneity poses a particular problem for tests that are based on genetic linkage (as opposed to direct detection of mutations). Genetic linkage can only be used to make a diagnosis by inference. If there are two forms of the disease, one linked and one unlinked to a particular genetic marker, and if there is no way to distinguish between the two forms, an extensive pedigree analysis is required to confirm linkage to the marker in each family before a reliable diagnosis can be made. This inevitably involves the participation of many family members. Again, the ethical implications of such studies are far reaching. Is a physician entitled to approach the relatives of the patient in order for such a diagno-

sis to be made? If the physician does approach the relatives, what responsibilities does he or she have for the effect that participation in such testing may have on their lives? As the repertoire of tests grows, these questions will need to be addressed by every physician.

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Tumors of the Urinary Tract

TUMORS OF THE KIDNEY, ureter, and bladder are a source of major morbidity and mortality in the United States. It is estimated that more than 78,000 new cases will be diagnosed in 1992, accounting for 10% and 4% of new cancers in men and women, respectively. More than 20,000 deaths will result from these disorders. These are sobering figures, but cautious optimism is justified for improved therapeutic results in the 1990s. Improvements in diagnostic techniques, clearer understanding of molecular and chromosomal markers of biologic behavior, multimodality therapeutic approaches, and use of biologic therapies give hope for both better quality of life and improved survival.

Some important advances have been made in elucidating the molecular genetics of genitourinary cancers. For example, nonrandom chromosomal abnormalities occur in patients with renal carcinomas and, in selected instances, have led to screening of family members, early detection, and cure. Bilateral renal cancers in young patients and a strong family history should alert the internist and urologist alike to the possibility of an inherited genetic abnormality. Trisomy 7 occurs in a substantial number of urologic tumors, including renal carcinomas. Similarly, von Hippel-Lindau disease may be associated with a high frequency of renal cancers. The gene for von Hippel-Lindau disease has been mapped to an oncogene locus of chromosome 3p25. This chromosomal location may be important in the genesis of other cancers, including small-cell carcinoma and certain ovarian neoplasms.

Bladder cancer, too, is associated with many chromosomal alterations, including trisomy 7, monosomy 9, and alterations in chromosome 5. In selected instances, prognosis has been correlated with specific genetic alterations of the tumor. Indeed, in some centers specific therapies for superficial bladder cancer may be influenced by these "molecular markers."

In this month's issue of the journal, two well-respected and erudite leaders in urologic cancer, Drs See and Williams, review the current status of urinary tumors.[1] They provide a detailed overview of current methods of diagnosis and treatment and highlight areas of active investigation. Two specific topics deserve further comment.

There is a continued interest in a multimodality approach to managing invasive bladder cancer. Once the neoplasm has invaded the lamina propria and involves the muscularis, radical cystectomy has been the traditional treatment of choice. This procedure causes substantial morbidity. It requires an ostomy appliance and quite often results in impotence, due to the commonly performed accompanying prostatectomy. With advances in surgical technique, both of these complications can be minimized.

Creation of continent urinary pouches, using innovative surgical techniques, now obviates the need for complicated external ostomy appliances, and more centers are now using continence-sparing urinary diversions. Likewise, improvements in the anatomic delineation of the nervous and vascular supply to the male genitalia have resulted in surgical techniques (nerve-sparing procedures) that preserve potency.

Systemic chemotherapy of metastatic bladder cancer has also advanced, and slowly improved survival rate and substantial tumor shrinkages in both the primary cancer and metastases have been documented. In some patients these beneficial effects have persisted. The rationale for using chemotherapy for muscle invasive disease, aimed at "down staging" the tumor, is to preserve the bladder while eliminating any accompanying micrometastatic disease. Multimodality therapy consisting of "up-front" chemotherapy followed by radiation therapy delivered to the primary organ may prove to be a reasonable alternative to radical cystectomy in some patients, but further studies are required.

Renal cell carcinoma, sometimes dubbed "the internist's tumor," is nicely reviewed by See and Williams. Early diagnosis greatly increases curability in this disease. Patients who are fortunate enough to have an incidental mass found during an evaluation for nonkidney-related problems generally have a more favorable prognosis when compared with those first diagnosed with paraneoplastic syndromes or symptoms related to metastases. Unfortunately, the therapy for advanced forms of renal cell cancer has not greatly improved. Biologic response modifiers, such as interleukin-2, interferon, and tumor necrosis factor, have proliferated, but most patients do not benefit greatly from use of these agents. As we begin to understand the biology of renal cell cancer better, we should begin to apply to larger patient populations the few therapies that are effective in selected patients.

In the next decade, many diverse biologic preparations will be available for treating human cancer. The use of single agents has generally been disappointing so far. Now, however, we are beginning to appreciate and to understand the multiple actions of biologic therapies and are finally able to evaluate such therapies in the clinic. We have powerful tools to diagnose and stage renal cell cancer, as reviewed so nicely in this issue of the journal. The next few years should bring correspondingly effective therapies for treating renal cancer that has spread beyond the confines of the kidney.

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